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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,072	01/25/2002	Genoveffa Franchini	1662.018US1	1664

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/048,072	FRANCHINI ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10 and 12-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-10 and 12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/05/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 05 September, 2006. New claims 19 and 20 accompanied the response. Claims 1-3, 5-10, and 12-20 are currently under examination.

37 C.F.R. § 1.98

The information disclosure statement filed 05 September, 2006, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, Second Paragraph

The previous rejection of claims 1-3, 5-10, and 12-18 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicants' amendment.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 5-10, and 12-20 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is directed toward a method of stimulating an HIV-1-specific protective $CD8^+$ immune response in an infected human by administering a recombinant virus encoding HIV immunogens carrying CTL epitopes. Claim 18 is directed toward a method of maintaining a reduced viral load in any given mammal infected with an immunodeficiency virus by administering a recombinant virus encoding retroviral peptides containing CTL epitopes wherein said peptides are capable of inducing a protective $CD8^+$ HIV antigen response. Claims 19 and 20 are directed toward methods of inducing an HIV-1-specific protective CD8+ immune response in an infected human by administering a recombinant virus encoding HIV peptides containing CTL epitopes.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146

U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide sufficient guidance pertaining to those HIV or retroviral immunogens that are capable of inducing protective HIV-specific $CD8^+$ immune responses. The claims are broadly directed toward any recombinant viral vaccine encoding a peptides obtained from HIV or retroviral Gag, Pol, Env, or Nef proteins. Claim 19 provides absolutely no guidance pertaining to the immunogen of interest. The disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating protective HIV-specific $CD8^+$ immune responses. Which HIV or retroviral proteins/polypeptides contain protective CTL epitopes? Which viral constructs are capable of expressing the immunogens of interest for a sufficient period of time to induce an HIV-specific $CD8^+$ immune response of the proper specificity, titer, and duration? The claimed invention basically requires that the skilled artisan guess as to which constructs and immunogens will provide the desired immune response.

2) The disclosure fails to provide sufficient guidance pertaining to the correlates of human protection. Currently, the correlates of human protection remain to be elucidated. To date, it is not clear what type of immune response is required to provide a therapeutic or protective benefit. As Pantaleo and Koup (2004) note (see left col., p. 808) "There is still no direct experimental evidence...that HIV-1-specific cellular immunity prevents disease progression." There appears to be some suggestion that **both** polyfunctional (IL-2 and IFN-γ) $CD4^+$ and viral-specific $CD8^+$ T-cell responses are involved. The disclosure fails to address either of these considerations. Moreover, $CD8^+$ T-cell responses by definition are **not** protective in nature. CTL

vaccines do not prevent infection, but rather control the spread of virus. As McMichael and Hanke (2003) state (see left col., p. 876) "Whereas neutralizing antibodies can prevent infection, $CD8^+$ T-cell responses cannot. These cytotoxic T lymphocytes (CTLs) react to other cells of the body that are infected by HIV and present peptide fragments of viral proteins bound to MHC class I proteins." The authors further conclude that "A vaccine should stimulate high numbers of $CD8^+$ T memory cells, which rapidly release cytokines and chemokines on subsequent antigen contact and start killing target cells (Fig. 2). But these cells may need to be expanded to out-number the virus-infected cells and distributed to several sites around the body. Thus, full antiviral activity may take days to develop and will only control, rather than prevent, viral infection." The specification is silent concerning these issues.

3) The disclosure fails to provide sufficient guidance pertaining to the *quasispecies* nature of HIV infection that ultimately leads to viral evasion and escape. The plasticity of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of an effective vaccine. HIV-1 exists as a large pool of genotypically and phenotypically distinct isolates. It has been well-documented that the virus relies upon this heterogeneity to escape immune surveillance and detection (McMichael and Hanke, 2003). For instance, the majority of the neutralizing antibody response is directed toward a molecular determinant (V3) that undergoes rapid mutation. Thus, even when a neutralizing antibody or $CD8^+$ response is generated, it rapidly becomes ineffective as other members of the *quasispecies* quickly replicate and grow out. The disclosure fails to provide any guidance concerning the identification of HIV or retroviral CTL epitopes that are resistant to viral escape.

4) The disclosure fails to provide any working embodiments. As noted *supra*, the claims encompass considerable breadth pertaining to the viral construct (i.e., source of viral expression vector, HIV/retroviral immunogens expressed). The only examples provided in the specification are purely prophetic and fail to provide any meaningful data. Some data was provided from a macaque model, however, this model is not an art-recognized model for vaccine development. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies cannot be directly extrapolated to a clinical setting due to the structural differences between SIV and HIV (Haigwood, 2004). As Haigwood (2004) concludes (see abstract, p. 187) "By necessity, animal models can only be validated after successful trials in humans and the determination of correlates of protection. Because the only vaccine product tested in phase III trials in humans failed to achieve the desired protective threshold, we are as yet unable to validate any of the currently used nonhuman primate models for vaccine research." Pantaleo and Koup (2004) also concluded (see right col., p. 809) that "it is also unclear what data from which animal model of HIV-1 infection are most relevant to human infection and vaccine protection." Additional limitations pertaining to the macaque model were reviewed by Feinberg and Moore (2002) who note (see left col., p. 207) that "because HIV-1 does not productively infect macaques, it cannot be used as a challenge virus to assess whether a given vaccine can prevent or ameliorate infection[1,2]. Hence, preclinical AIDS vaccine models rarely test the identical vaccine constructs that are planned for human use. Instead, studies in rhesus macaques explore the potential protective efficacy of vaccine

concepts, not the actual vaccines being developed for human trials."

5) The state-of-the-art vis-à-vis HIV CTL vaccine development can be characterized by unpredictability (Haynes *et al.*, 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, 2004; Burton and Moore, 1998; Pantaleo and Koup, 2004; Haigwood, 2004; Altes *et al.*, 2002; McMichael and Hanke, 2003; Feinberg and Moore, 2002; Stott and Almond, 1995). To date, there is not one single effective HIV CTL vaccine on the market. Several clinical trials have been conducted but in every situation, the immunogen failed to induce a long-lasting and high-titer immune response. Common problems encountered with vaccine development include the extraordinary variability, or *quasispecies* nature of HIV, the lack of an exact animal model of HIV-induced AIDS, and the lack of understanding of the correlates of protective immunity. The disclosure fails to address these concerns. Moreover, applicants are reminded that enablement is determined as of the effective filing date of the application (28 July, 1999). *Chiron Corp.* v. *Genentech Inc.*, 363 F.3d 1247, 1254, 70 U.S.P.Q.2d 1321, 1325-26 (Fed. Cir. 2004). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 U.S.P.Q. 402,405-06 (C.C.P.A. 1976); *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976).

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Response to Arguments

Applicants submit that the disclosure provides a number of examples demonstrating that the invention has been successfully practiced in a recognized animal model of HIV-1 infection. First, as clearly set forth *supra*, direct extrapolations cannot be made between results obtained in the macaque model and protective or therapeutic efficacy in humans. Haigwood (2004) clearly addresses this issue and notes that macaque models are not predictive at this point in time. While they are useful for evaluating vaccine concepts, they seldom test the same vaccine construct employed in humans. The data provided by applicants involves a limited number of constructs (e.g., all highly attenuated pox virus strains (e.g., NYVAC, ALVAC, and MVA) encoding SIV structural antigens (e.g., Gag, Pol, Env). Applicants are reminded that the claims are not directed toward any particular vector construct. Moreover, the immunogens employed in this study were all obtained from SIV. Applicants have failed to identify whether corresponding therapeutic epitopes are present in HIV. Finally, as set forth *supra*, none of these studies provided evidence of a protective $CD8^+$ T-cell response. At best, they provide support for the generation of therapeutic $CD8^+$ T-cell responses in macaques under the conditions studied.

It was again argued that the claimed methods are useful in humans based upon a previously filed declaration by Dr. Franchini (16 May, 2005). The content of this declaration has already been addressed. Dr. Franchini indicated that preliminary results have been obtained from a clinical trial involving ACTG5054 which is an **ALVAC** recombinant encoding **Gag**, **PR**, and **Env**. Applicants noted that a reduction in viral load was observed in this study. Applicants are again reminded that

the claims are not directed toward any particular expression vector or HIV/retroviral epitope. Considering the unpredictability of the prior art, a single example would be insufficient to enable the full breadth of the claimed invention.

Applicants further argued that Jin *et al.* (2002) provide further evidence that the claimed invention is enabled. The data in this study is insufficient to support the full breadth of the claimed invention. First, this study employed a single attenuated pox virus construct (e.g., ALVAC) encoding the recited immunogens. Applicants are again reminded of the breadth of the claim language which is not limited to any particular viral construct of combination of HIV/retroviral immunogens. Second, the data contained in this study simply measured HIV-1-specific $CD8^+$ T-cell proliferative responses. As set forth in Table 2, many of the responses were variable and weak. Only five of fourteen patients displayed moderate proliferation. Eight of fourteen patients displayed no or limited proliferative responses. Thus, contrary to applicants' assertion, the vaccine did not generate a strong HIV-1-specific $CD8^+$ T-cell response in the majority of patients studies. Moreover, the data fails to demonstrate that the HIV-1-specific $CD8^+$ T-cell response generated was of sufficient magnitude, specificity, and duration to provide a meaningful therapeutic response. Third, the study involved patients that were aggressively treated with HAART following recent infections. These subjects displayed viral suppression for a period of over two years. Thus, it is not readily manifest how applicable these results are to chronically infected patients. Moreover, in summarizing their work, Jin and colleagues reported (see right col., p. 2214) that "the limited magnitude of the $CD8^+$ T-

cell response and the lack of persistence of T helper cell responses may limit the utility of this particular immunogen in this clinical setting."

Additional evidence was provided in the form of an article published by Hel *et al.* (2006). Once again this article employed a highly attenuated poxvirus (e.g., NYVAC) encoding SIV structural (e.g., Gag, Pol, and Env) and non-structural immunogens (e.g., Tat, Rev, and Nef). Interestingly, this article reported that the vaccine constructs of interest actually reduced $CD8^+$ T-cell responses to Gag, Env, Tat, and Nef suggesting that there are limits to the size of both $CD4^+$ and effector $CD8^+$ T-cell populations. Since this article involved a single vector and SIV immunogens, it suffers from the same limitations discussed *supra*. The authors also reported (see left col., p. 94) that "Although the immunization with early proteins alone delayed the onset of viremia, the benefit was rapidly lost, probably due to virus escape from immune recognition." Thus, it is not readily manifest that the desired immune response can be maintained for a sufficient duration to actually provide a meaningful response.

Applicants further submit that the claimed vaccines overcome the quasispecies nature of HIV infection that frequently leads to immune evasion. This argument is clearly not convincing. None of the data provided in the specification of declaratory form addresses viral escape. In fact, Hel *et al.* (2006) actually suggest that this is a problem in SIV as discussed in the preceding paragraph. All of applicants arguments have been carefully considered but are not deemed to be persuasive.

Finality of Office Action

Applicants' amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d)

transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

26 November, 2006